PTO/SB/53 (02-01)
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REISSUE APPLICATION: CONSENT OF ASSIGNEE; STATEMENT OF NON-ASSIGNMENT	Docket Number (Optional) PROV1100-1

This is part of the application for a reissue patent based on the original patent identified below.

Name of Patentee(s) **Robert E. Krall, Charles W. Kerber, and Kimberly Knox**

Patent Number **6,037,366**	Date Patent Issued **March 14, 2000**

Title of Invention **COMPOSITION FOR CREATING VASCULAR OCCLUSIONS**

1. [X] Filed herein is a statement under 37 CFR 3.73(b). (Form PTO/SB/96)

2. [ ] Ownership of the patent is in the inventor(s), and no assignment of the patent is in effect.

One of boxes 1 or 2 above must be checked. If multiple assignees, complete this form for each assignee. If box 2 is checked, skip the next entry and go directly to "Name of Assignee".

The written consent of all assignees and inventors owning an undivided interest in the original patent is included in this application for reissue.

The assignee(s) owning an undivided interest in said original patent is/are **PROHOLD MEDICAL TECHNOLOGIES, INC.** and the assignee(s) consents to the accompanying application for reissue.

Name of assignee/inventor (if not assigned)

Signature	Date 3/30/01

Typed or printed name and title of person signing for assignee (if assigned)

Gary L. Loomis
Vice President, Research & Development

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REISSUE APPLICATION DECLARATION BY THE INVENTOR	Docket Number (Optional) PROV1100-1

As a below named inventor, I hereby declare that:
My residence, mailing address and citizenship are stated below next to my name.
I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is described and claimed in patent number 6,037,366, granted March 14, 2000, and for which a reissue patent is sought on the invention entitled COMPOSITION FOR CREATING VASCULAR OCCLUSIONS,
the specification of which

☒ is attached hereto.

☐ was filed on _____ as reissue application number _____/_____

and was amended on _____.
(If applicable)

I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment referred to above.
I acknowledge the duty to disclose information which is material to patentability as defined in 37 CFR 1.56.
I verily believe the original patent to be wholly or partly inoperative or invalid, for the reasons described below. (Check all boxes that apply.)

☒ by reason of a defective specification or drawing.

☒ by reason of the patentee claiming more or less than he had the right to claim in the patent.

☐ by reason of other errors.

At least one error upon which reissue is based is described below. If the reissue is a broadening reissue, such must be stated with an explanation as to the nature of the broadening:

See attached Reissue Application Declaration by the Inventor of Robert E. Krall (4 pgs.), Charles W. Kerber (4 pgs.) and Kimberly Knox (4 pgs.)

PTO/SB/51 (02-01)
Approved for use through 01/31/2004. OMB 0651-0033
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(REISSUE APPLICATION DECLARATION BY THE INVENTOR, page 2)

Docket Number (Optional) PROV1100-1

All errors corrected in this reissue application arose without any deceptive intention on the part of the applicant. As a named inventor, I hereby appoint the following attorney(s) and/or agent(s) to prosecute this application and transact all business in the United States Patent and Trademark Office connected therewith.

Name(s)	Registration Number
Lisa A. Haile, J.D., Ph.D.	38,347

Correspondence Address: Direct all communications about the application to:

X	Customer Number	28213 *Type Customer Number here*	→	*Place Customer Number Bar Code Label here*

	Firm or Individual Name	LISA A. HAILE, PH.D. GRAY CARY WARE & FREIDENRICH LLP				
Address		SUITE 1600				
Address		4365 EXECUTIVE DRIVE,				
City		SAN DIEGO	State	CA	Zip	92121-2189
Country		UNITED STATES OF AMERICA				
Telephone		(858) 677-1456	Fax	(858) 677-1465		

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine and imprisonment, or both, under 18 U.S.C. 1001, and that such willful false statements may jeopardize the validity of the application, any patent issuing thereon, or any patent to which this declaration is directed.

Full name of sole or first inventor (given name, family name)
Robert E. Krall

Inventor's signature	Dates
Robert E. Krall	3/22/01
Residence 2728 Via Dieguenos, Alpine, California 91901	**Citizenship** United States
Mailing Address Same	

Full name of second joint inventor (given name, family name)
Charles W. Kerber

Inventor's signature	Dates
Charles Kerber	22 Mar 2001
Residence 4444 Tapa Tapa Drive, La Mesa, California 91941-7160	**Citizenship** United States
Mailing Address	

Full name of second third inventor (given name, family name)
Kimberly Knox

Inventor's signature	Dates
Kimberly Knox	3/23/01
Residence 4444 Tapa Tapa Drive, La Mesa, California 91941-7160	**Citizenship** United States
Mailing Address	

☐ Additional joint inventors are named on separately numbered sheets attached hereto.

Gray Cary\GT\6229496.1
105458-4

PATENT
ATTORNEY DOCKET NO.: PROV1100-1

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Name of Patentees: Krall et al.
Patent No.: 6,037,366 Date Patent Issued: March 14, 2000
Title of Invention: COMPOSITION FOR CREATING VASCULAR OCCULSIONS

BOX REISSUE
Commissioner for Patents
Washington, D.C. 20231

REISSUE APPLICATION DECLARATION BY THE INVENTOR ROBERT E. KRALL

I, Robert E. Krall hereby declare as follows:

1) My residence is: 2728 Via Dieguenos, Alpine, CA 91901

2) I am a citizen of the United States of America

3) I have been an employee of Prohold Medical Technologies, Inc., now Provasis Therapeutics, Inc., since Sept. 1995.

4) On about February 15, 2001, I became aware that the claims of issued U.S.Pat. No. 6,037,366 render that patent partly inoperative because we claimed less in that patent than we had the right to claim.

5) Amended and new claims to U.S.Pat. No. 6,037,366 are set forth in this reissue application submission. These claims are supported by the specification and contain matter that we were entitled to claim originally. The new claims do not contain any new matter.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In independent claims 1 and 5, the ethyl myristate claimed as an element of the composition should have been more broadly claimed as "a fatty acid ester." The polymer of 2-hexylcyanoacrylate should read "stabilized," rather than "sterilized." Part 2 of the composition should not contain the language "a weak aqueous bicarbonate solution."

Ethyl myristate is a type of fatty acid ester. The specification discloses that, "any of the large chain fatty acid esters will work to replace ethyl myristate" (col. 2, lines 1-3. *See also* col. 3, lines 47-50). The broader class of fatty acid esters should have been claimed in the original claims to this invention.

In the specification, the polymer of part 2 of the composition is shown to be stabilized and sterilized simultaneously. (col. 2, lines 24-26.) The resulting polymer is stable. The polymer in this stable state was available to be claimed in the claims of the original application, but was not. Therefore the language describing the polymer of 2-hexyl cyanoacrylate should read "stabilized," rather than "sterilized."

The composition claimed in U.S.Pat. No. 6,037,366 includes the language "in a weak aqueous bicarbonate solution" with respect to part 2. As can be seen in column 2, lines 10-14, the weak aqueous bicarbonate solution is used in the preparation of the polymer that is part of the claimed composition. However, the weak aqueous bicarbonate solution is not itself an element

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

in claimed composition. Therefore, we are requesting removal of the language "in a weak aqueous bicarbonate solution" from claims 1 and 5.

The language of dependent claim 3 has been amended to reflect the changes in claims 1 and 2, from which it depends.

Additionally, in claim 5, part (b), the mixture does not necessarily have to be injected. Many methods of delivery are available. The specification of the present invention simply discusses "the delivered product," (col. 2, lines 51-62) but not specific methods of delivery. Claim 5 has been broadened to recite "administering."

In claim 5, the language "with the gold metal powder suspended in the mixture" has been deleted. While this is a characteristic disclosed in the specification, it is not necessary to the invention. Therefore that language has been removed from part (b) of claim 5.

New claims 6 to 16 have been added. These claims provide further protection for the invention, but do not add any new matter. Independent claims 6 and 11 are directed to the previously unclaimed broad inventive concept of the invention, as set forth in the specification. Support for claim 6 can be found in the specification at, for example, col. 1, lines 59-61, col. 1, lines 66 to col. 2, line 4, col. 2, lines 24-26, and col. 3, lines 42-45. Support for claim 11 can be found in the specification at, for example, col. 1, lines 51-52, col. 1, line 59 to col. 2, line 3, and col. 2, lines 34-38. Dependent claims 7 to 10 and 12 to 16 are directed to additionally disclosed,

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

but previously unclaimed, features of the broad inventive concept. These claims are supported by the specification. Support for claim 7 and 12 can be found in the specification at, for ex., col. 1, lines 64-65 and col. 3, lines 19-24. Support for claim 8 and 13 can be found in the specification at, for ex., col. 3, lines 42-45. Support for claims 9 and 15 can be found in the specification at, for example, col. 2, lines 34-36. Support for 10 and 14 can be found in the specification at, for example, col. 2, lines 1-3. Support for claim 16 can be found in the specification at, for example, col. 1, lines 50-51.

During the prosecution of the Application, the full scope of the invention as it relates to the elements of the claimed composition was not appreciated by me or my Attorneys. The claims as submitted in this reissue application more broadly and more fully claim the disclosed invention.

Robert E. Krall

ROBERT E. KRALL

3/22/01

Date

PATENT
ATTORNEY DOCKET NO.: PROV1100-1

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Name of Patentees: Krall et al.
Patent No.: 6,037,366 Date Patent Issued: March 14, 2000
Title of Invention: COMPOSITION FOR CREATING VASCULAR OCCULSIONS

BOX REISSUE
Commissioner for Patents
Washington, D.C. 20231

REISSUE APPLICATION DECLARATION BY THE INVENTOR CHARLES W. KERBER

I, Charles W. Kerber hereby declare as follows:

1) My residence is: 4444 ~~Tapa Tapa~~ Topa Topa 3/23/01 CK Drive, La Mesa, CA 91941-7160.

2) I am a citizen of the United States of America

3) I have been an employee of Prohold Medical Technologies, Inc., now Provasis Therapeutics, Inc., since October, 1995.

4) On or about February 15, 2001, I became aware that the claims of issued U.S.Pat. No. 6,037,366 render that patent partly inoperative because we claimed less in that patent than we had the right to claim.

5) Amended and new claims to U.S.Pat. No. 6,037,366 are set forth in this reissue application submission. These claims are supported by the specification and contain matter that we were entitled to claim originally. The new claims do not contain any new matter.

In independent claims 1 and 5, the ethyl myristate claimed as an element of the composition should have been more broadly claimed as "a fatty acid ester." The polymer of 2-

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

hexylcyanoacrylate should read "stabilized," rather than "sterilized." Part 2 of the composition should not contain the language "a weak aqueous bicarbonate solution."

Ethyl myristate is a type of fatty acid ester. The specification discloses that, "any of the large chain fatty acid esters will work to replace ethyl myristate" (col. 2, lines 1-3. *See also* col. 3, lines 47-50). The broader class of fatty acid esters should have been claimed in the original claims to this invention.

In the specification, the polymer of part 2 of the composition is shown to be stabilized and sterilized simultaneously. (col. 2, lines 24-26.) The resulting polymer is stable. The polymer in this stable state was available to be claimed in the claims of the original application, but was not. Therefore the language describing the polymer of 2-hexyl cyanoacrylate should read "stabilized," rather than "sterilized."

The composition claimed in U.S.Pat. No. 6,037,366 includes the language "in a weak aqueous bicarbonate solution" with respect to part 2. As can be seen in column 2, lines 10-14, the weak aqueous bicarbonate solution is used in the preparation of the polymer that is part of the claimed composition. However, the weak aqueous bicarbonate solution is not itself an element in the claimed composition. Therefore we are requesting removal of the language "in a weak aqueous bicarbonate solution" from claims 1 and 5.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

The language of dependent claim 3 has been amended to reflect the changes in claims 1 and 2, from which it depends.

Additionally, in claim 5, part (b), the mixture does not necessarily have to be injected. Many methods of delivery are available. The specification of the present invention simply discusses "the delivered product," (col. 2, lines 51-62) but not specific methods of delivery. Claim 5 has been broadened to recite "administering."

In claim 5, the language "with the gold metal powder suspended in the mixture" has been deleted. While this is a characteristic disclosed in the specification, it is not necessary to the invention. Therefore that language has been removed from part (b) of claim 5.

New claims 6 to 16 have been added. These claims provide further protection for the invention, but do not add any new matter. Independent claims 6 and 11 are directed to the previously unclaimed broad inventive concept of the invention, as set forth in the specification. Support for claim 6 can be found in the specification at, for example, col. 1, lines 59-61, col. 1, lines 66 to col. 2, line 4, col. 2, lines 24-26, and col. 3, lines 42-45. Support for claim 11 can be found in the specification at, for example, col. 1, lines 51-52, col. 1, line 59 to col. 2, line 3, and col. 2, lines 34-38. Dependent claims 7 to 10 and 12 to 16 are directed to additionally disclosed, but previously unclaimed, features of the broad inventive concept. These claims are supported by the specification. Support for claim 7 and 12 can be found in the specification at, for ex., col.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

1, lines 64-65 and col. 3, lines 19-24. Support for claim 8 and 13 can be found in the specification at, for ex., col. 3, lines 42-45. Support for claims 9 and 15 can be found in the specification at, for example, col. 2, lines 34-36. Support for 10 and 14 can be found in the specification at, for example, col. 2, lines 1-3. Support for claim 16 can be found in the specification at, for example, col. 1, lines 50-51.

During the prosecution of the Application, the full scope of the invention as it relates to the elements of the claimed composition was not appreciated by me or my Attorneys. The claims as submitted in this reissue application more broadly and more fully claim the disclosed invention.

Charles Kerber

CHARLES W. KERBER

22 March 2001

Date

PATENT
ATTORNEY DOCKET NO.: PROV1100-1

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Name of Patentees: Krall et al.
Patent No.: 6,037,366 Date Patent Issued: March 14, 2000
Title of Invention: COMPOSITION FOR CREATING VASCULAR OCCULSIONS

BOX REISSUE
Commissioner for Patents
Washington, D.C. 20231

REISSUE APPLICATION DECLARATION BY THE INVENTOR KIMBERLY KNOX

I, Kimberly Knox hereby declare as follows:

1) My residence is: 4444 ~~Tapa Tapa~~ Topa Topa Dr 3/23/01 Drive, La Mesa, CA 91941-7160.

2) I am a citizen of the United States of America

3) I have been an employee of Prohold Medical Technologies, Inc., now Provasis Therapeutics, Inc., since October, 1995.

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

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Ethyl myristate is a type of fatty acid ester. The specification discloses that, "any of the large chain fatty acid esters will work to replace ethyl myristate" (col. 2, lines 1-3. *See also* col. 3, lines 47-50). The broader class of fatty acid esters should have been claimed in the original claims to this invention.

In the specification, the polymer of part 2 of the composition is shown to be stabilized and sterilized simultaneously. (col. 2, lines 24-26.) The resulting polymer is stable. The polymer in this stable state was available to be claimed in the claims of the original application, but was not. Therefore the language describing the polymer of 2-hexyl cyanoacrylate should read "stabilized," rather than "sterilized."

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

The language of dependent claim 3 has been amended to reflect the changes in claims 1 and 2, from which it depends.

Additionally, in claim 5, part (b), the mixture does not necessarily have to be injected. Many methods of delivery are available. The specification of the present invention simply discusses "the delivered product," (col. 2, lines 51-62) but not specific methods of delivery. Claim 5 has been broadened to recite "administering."

In claim 5, the language "with the gold metal powder suspended in the mixture" has been deleted. While this is a characteristic disclosed in the specification, it is not necessary to the invention. Therefore that language has been removed from part (b) of claim 5.

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

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During the prosecution of the Application, the full scope of the invention as it relates to the elements of the claimed composition was not appreciated by me or my Attorneys. The claims as submitted in this reissue application more broadly and more fully claim the disclosed invention.

KIMBERLY KNOX

03/23/01
Date

PATENT
ATTORNEY DOCKET NO.: PROV1100-1

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Name of Patentees: Krall et al.
Patent No.: 6,037,366 Date Patent Issued: March 14, 2000
Title of Invention: COMPOSITION FOR CREATING VASCULAR OCCULSIONS

BOX REISSUE
Commissioner for Patents
Washington, D.C. 20231

POWER OF ATTORNEY BY ASSIGNEE

As a below-named assignee of the above-identified application ("Application"):

I hereby appoint the following attorneys of the assignee to prosecute the Application and to transact all business in the United States Patent and Trademark Office connected therewith:

TIM ELLIS	Registration No. 41,734
LISA A. HAILE	Registration No. 38,347
RICHARD J. IMBRA	Registration No. 37,643
SHEILA R. KIRSCHENBAUM	Registration No. 44,835
JUNE M. LEARN	Registration No. 31,238
TIMOTHY W. LOHSE	Registration No. 35,255
TERRANCE A. MEADOR	Registration No. 30,298
STEVEN R. SPRINKLE	Registration No. 40,825
BARRY N. YOUNG	Registration No. 27,744

PATENT
ATTORNEY DOCKET NO.: PROV1100-1

Name of Patentees: Krall et al.
Patent No.: 6,037,366 Date Patent Issued: March 14, 2000
Title of Invention: COMPOSITION FOR CREATING VASCULAR OCCULSIONS
Page 2

I hereby authorize and request insertion of the application number of the Application when officially known.

Direct all telephone calls to:

LISA A. HAILE, J.D., PH.D.
Telephone: (858) 677-1456

Address all correspondence to:

LISA A. HAILE, J.D., PH.D.
GRAY CARY WARE & FREIDENRICH LLP
4365 Executive Drive, Suite 1600
San Diego, CA 92121

PROVASIS THERAPUETICS, INC.

By: _____

Name: Gary L. Loomis

Title: Vice President, Research & Development

Date: March 30, 2001

Gray Cary\GT\6229559.1
105458-4

PTO/SB/51 (02-01)
Approved for use through 01/31/2004. OMB 0651-0033
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

REISSUE APPLICATION DECLARATION BY THE INVENTOR

Docket Number (Optional)

PROV1100-2

As a below named inventor, I hereby declare that:

My residence, mailing address and citizenship are stated below next to my name.

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is described and claimed in patent number 6,037,366, granted March 14, 2000, and for which a reissue patent is sought on the invention entitled COMPOSITION FOR CREATING VASCULAR OCCULSIONS, the specification of which

☐ is attached hereto.

☒ was filed on March 30, 2001 as reissue application number 09/823,775 and was amended on November 5, 2003.

I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment referred to above.
I acknowledge the duty to disclose information which is material to patentability as defined in 37 CFR 1.56.

I verily believe the original patent to be wholly or partly inoperative or invalid, for the reasons described below. (Check all boxes that apply.)

☐ by reason of a defective specification or drawing.

☒ by reason of the patentee claiming more or less than he had the right to claim in the patent.

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(REISSUE APPLICATION DECLARATION BY THE INVENTOR, page 2)

Docket Number (Optional)
PROV1100-2

All errors corrected in this reissue application arose without any deceptive intention on the part of the applicant. As a named inventor, I hereby appoint the following attorney(s) and/or agent(s) to prosecute this application and transact all business in the United States Patent and Trademark Office connected therewith.

Name(s)	Registration Number
Lisa A. Haile, J.D., Ph.D.	38,347

Correspondence Address: Direct all communications about the application to:

X	Customer Number	28213 *Type Customer Number here*	→	*Place Customer Number Bar Code Label here*

	Firm or Individual Name	LISA A. HAILE, PH.D. GRAY CARY WARE & FREIDENRICH LLP				
Address		SUITE 1100				
Address		4365 EXECUTIVE DRIVE,				
City		SAN DIEGO	State	CA	Zip	92121-2133
Country		UNITED STATES OF AMERICA				
Telephone		(858) 677-1456	Fax	(858) 677-1465		

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine and imprisonment, or both, under 18 U.S.C. 1001, and that such willful false statements may jeopardize the validity of the application, any patent issuing thereon, or any patent to which this declaration is directed.

Full name of sole or first inventor (given name, family name)
Robert E. Krall

Inventor's signature	Date
Robert E. Krall	4/21/04
Residence 2728 Via Dieguenos, Alpine, California 91901	Citizenship United States yes
Mailing Address	

Full name of second joint inventor (given name, family name)
Charles W. Kerber

Inventor's signature	Date
Residence 4444 Topa Topa Drive, La Mesa, California 91941	Citizenship United States
Mailing Address	

Full name of second third inventor (given name, family name)
Kimberly Knox

Inventor's signature	Date
Residence 4444 Topa Topa Drive, La Mesa, California 91941	Citizenship United States
Mailing Address	

☐ Additional joint inventors are named on separately numbered sheets attached hereto.

PTO/SB/51 (02-01)
Approved for use through 01/31/2004. OMB 0651-0033
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

REISSUE APPLICATION DECLARATION BY THE INVENTOR

Docket Number (Optional)

PROV1100-2

As a below named inventor, I hereby declare that:

My residence, mailing address and citizenship are stated below next to my name.

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is described and claimed in patent number 6,037,366, granted March 14, 2000, and for which a reissue patent is sought on the invention entitled COMPOSITION FOR CREATING VASCULAR OCCULSIONS, the specification of which

☐ is attached hereto.

☒ was filed on March 30, 2001 as reissue application number 09/823,775 and was amended on November 5, 2003.

I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment referred to above.
I acknowledge the duty to disclose information which is material to patentability as defined in 37 CFR 1.56.

I verily believe the original patent to be wholly or partly inoperative or invalid, for the reasons described below. (Check all boxes that apply.)

☐ by reason of a defective specification or drawing.

☒ by reason of the patentee claiming more or less than he had the right to claim in the patent.

☐ by reason of other errors.

At least one error upon which reissue is based is described below. If the reissue is a broadening reissue, such must be stated with an explanation as to the nature of the broadening:

PTO/SB/51 (02-01)
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(REISSUE APPLICATION DECLARATION BY THE INVENTOR, page 2)

Docket Number (Optional)
PROV1100-2

All errors corrected in this reissue application arose without any deceptive intention on the part of the applicant. As a named inventor, I hereby appoint the following attorney(s) and/or agent(s) to prosecute this application and transact all business in the United States Patent and Trademark Office connected therewith.

Name(s)	Registration Number
Lisa A. Haile, J.D., Ph.D.	38,347

Correspondence Address: Direct all communications about the application to:

X	Customer Number	28213 *Type Customer Number here*	→	*Place Customer Number Bar Code Label here*

	Firm or Individual Name	LISA A. HAILE, PH.D.				
		GRAY CARY WARE & FREIDENRICH LLP				
Address		SUITE 1100				
Address		4365 EXECUTIVE DRIVE,				
City		SAN DIEGO	State	CA	Zip	92121-2133
Country		UNITED STATES OF AMERICA				
Telephone		(858) 677-1456	Fax	(858) 677-1465		

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine and imprisonment, or both, under 18 U.S.C. 1001, and that such willful false statements may jeopardize the validity of the application, any patent issuing thereon, or any patent to which this declaration is directed.

Full name of sole or first inventor (given name, family name)
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Inventor's signature	Date
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Mailing Address	

Full name of second joint inventor (given name, family name)
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Mailing Address	

☐ Additional joint inventors are named on separately numbered sheets attached hereto.

*0556734

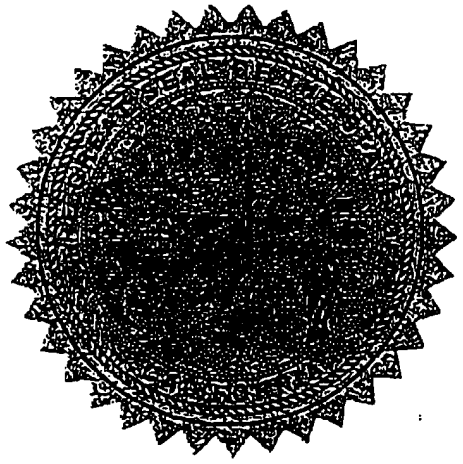
State of California

OFFICE OF THE SECRETARY OF STATE

SECRETARY OF STATE

I, *BILL JONES*, Secretary of State of the State of California, hereby certify:

That the attached transcript of 1 page(s) has been compared with the record on file in this office, of which it purports to be a copy, and that it is full, true and correct.



IN WITNESS WHEREOF, I execute this certificate and affix the Great Seal of the State of California this day of

DEC 15 2000

Bill Jones

Secretary of State

Sec/State Form CE-107 (rev. 8/98)

OSP 98 12524

A055[redacted]4

DO NOT WRITE IN THIS SPACE

AMENDED STATEMENT BY FOREIGN CORPORATION

ENDORSED - FILED
in the office of the Secretary of State
of the State of California

DEC 0 7 2000

BILL JONES, Secretary of State

Provasis Therapeutics Inc., a corporation organized and existing under the laws of Delaware and which is presently qualified for the transaction of intrastate business in the State of California, makes the following statement:

That the name of the corporation has been changed to that hereinabove set forth and that the name relinquished at the same time of such change was Prohold Medical Corporation

Provasis Therapeutics Inc.
(Name of Corporation)

(Signature of Corporate Officer)

John W. Cardosa, Chief Financial Officer
(Typed Name and Title of Officer Signing)

OFFICE OF THE SECRETARY OF STATE

Gray Cary\GT\6212817.1
105458-159923

RECEIVED TIME MAR.29. 9:03AM

State of Delaware
Office of the Secretary of State

I, EDWARD J. FREEL, SECRETARY OF STATE OF THE STATE OF DELAWARE, DO HEREBY CERTIFY THE ATTACHED IS A TRUE AND CORRECT COPY OF THE CERTIFICATE OF AMENDMENT OF "PROHOLD MEDICAL CORPORATION", CHANGING ITS NAME FROM "PROHOLD MEDICAL CORPORATION" TO "PROVASIS THERAPEUTICS INC.", FILED IN THIS OFFICE ON THE SEVENTEENTH DAY OF NOVEMBER, A.D. 2000, AT 9 O'CLOCK A.M.

A FILED COPY OF THIS CERTIFICATE HAS BEEN FORWARDED TO THE KENT COUNTY RECORDER OF DEEDS.

Edward J. Freel, Secretary of State

3114023 8100

001581026

AUTHENTICATION: 0804286

DATE: 11-20-00

STATE OF DELAWARE
SECRETARY OF STATE
DIVISION OF CORPORATIONS
FILED 09:00 AM 11/17/2000
001581026 - 3114023

CERTIFICATE OF AMENDMENT OF RESTATED CERTIFICATE OF INCORPORATION OF PROHOLD MEDICAL CORPORATION.

Prohold Medical Corporation, a corporation organized and existing under and by virtue of the General Corporation Law of the State of Delaware, does hereby certify:

FIRST: That at a meeting of the Board of Directors, resolutions were duly adopted setting forth a proposed amendment to the Certificate of Incorporation of said corporation, declaring said amendment to be advisable and calling for a written consent of the stockholders of said corporation for consideration thereof. Pursuant to such resolutions, Article First of the Corporation's Certificate of Incorporation is amended and restated in its entirety as follows:

"I.

The name of the corporation is Provasis Therapeutics Inc. (the "Corporation" or the "Company")."

SECOND: That thereafter, pursuant to resolution of its Board of Directors, a written consent of the stockholders of said corporation was duly solicited and executed, pursuant to which the necessary number of shares as required by statute and by said corporation's Certificate of Incorporation, as amended, were voted in favor of the amendment.

THIRD: That said amendment was duly adopted in accordance with the provisions of Section 242 of the General Corporation Law of the State of Delaware.

IN WITNESS WHEREOF, said corporation has caused this certificate to be signed and attested by its duly authorized officer this 7th day of November, 2000.

By: _____
John W. Cardosa, Secretary

State of Delaware

Office of the Secretary of State

I, EDWARD J. FREEL, SECRETARY OF STATE OF THE STATE OF DELAWARE, DO HEREBY CERTIFY THE ATTACHED IS A TRUE AND CORRECT COPY OF THE CERTIFICATE OF AMENDMENT OF "PROHOLD MEDICAL CORPORATION", FILED IN THIS OFFICE ON THE FOURTEENTH DAY OF JUNE, A.D. 2000, AT 9 O'CLOCK A.M.

A FILED COPY OF THIS CERTIFICATE HAS BEEN FORWARDED TO THE KENT COUNTY RECORDER OF DEEDS.

Edward J. Freel, Secretary of State

3114023 8100

001302884

AUTHENTICATION: 0498049

DATE: 06-15-00

RECEIVED TIME MAR.29. 9:03AM

U[redacted]037366A

United States Patent [19]

Krall et al.

[11] Patent Number: 6,037,366

[45] Date of Patent: Mar. 14, 2000

[54] COMPOSITION FOR CREATING VASCULAR OCCLUSIONS

[75] Inventors: Robert E. Krall, Alpine; Charles W. Kerber; Kimberly Knox, both of LaMesa, all of Calif.

[73] Assignee: Prohold Medical Technologies, Inc., El Cajon, Calif.

[21] Appl. No.: 09/151,621

[22] Filed: Sep. 11, 1998

Related U.S. Application Data

[60] Provisional application No. 60/058,510, Sep. 11, 1997.

[51] Int. Cl.[7] A61K 31/275; A61K 31/12; A61K 31/05; A61K 33/24

[52] U.S. Cl. 514/527; 514/526; 514/690; 514/730; 514/558; 514/560; 514/824; 514/834; 514/930; 514/944; 514/970; 424/601; 424/605; 424/649; 424/78.08; 424/78.31; 424/78.37; 604/49; 604/53

[58] Field of Search 514/526, 527, 514/690, 730, 558, 560, 824, 834, 930, 944, 970; 424/601, 605, 649, 78.08, 78.31, 78.37; 604/49, 53

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Primary Examiner—John Pak

Attorney, Agent, or Firm—Campbell & Flores LLP

[57] ABSTRACT

A composition including 2-hexyl cyanoacrylate and gold is useful in treating arteriovenous malformations (AVMs) and other body lumens to be blocked.

5 Claims, No Drawings

COMPOSITION FOR CREATING VASCULAR OCCLUSIONS

This application claims the benefit of U.S. Provisional Application No. 60/058,510, filed on Sep. 11, 1997.

BACKGROUND OF THE INVENTION

1. Field of the Invention

This invention relates to a composition used to treat arteriovenous malformations ("AVMs") and other vascular abnormalities. The composition includes a cyanoacrylate liquid monomer and gold in a prepolymerized polymer of cyanoacrylate. The composition is placed into the body lumen via standard catheter procedures or directly percutaneously.

2. Description of the Related Art

AVMs and vascular tumors, especially those of the brain, are exceedingly difficult to treat. These growths may occur all over the body, but are especially difficult to treat when in the brain or brain stem. The composition of the invention is especially useful in treating neurological AVMs, but may also be used to treat tumors anywhere in the body.

Cyanoacrylate adhesives have been used surgically but are limited in their usefulness by cytotoxicity and heat generation. The brain is unusually sensitive to cytotoxicity and heat.

The art described in this section is not intended to constitute an admission that any patent, publication or other information referred to herein is "prior art" with respect to this invention, unless specifically designated as such. In addition, this section should not be construed to mean that a search has been made or that no other pertinent information as defined in 37 C.F.R. § 1.56(a) exists.

SUMMARY OF THE INVENTION

The invention provides a composition that may be placed in a body lumen including veins and arteries by super selective catheterization or direct puncture using standard tools of the interventional angiographer. The composition of the invention has been successfully tested in simulated models of the AVMs and tumors under fluoroscopy and in systems that closely resembles the neurological condition of the human body. Further studies have been done in the pig rete. The rete is a body of fine arteries that allows the blood to flow into the pig brain which closely resembles normal human AVMs.

The composition is a cyanoacrylate which involves mixing two separate containers of the material immediately prior to administration of the material into the AVM by catheter. The composition may contain seven ingredients which are divided into two parts prior to mixture and use. It furnishes properties that are useful for closing neurological AVMs. The product can also be used to close any growth resembling an AVM in any part of the body. Because of the sensitive nature of the tissues in the brain, the general sensitivity of the product must be controlled. In less sensitive areas, the product will work equally as well.

Part I consists of a cyanoacrylate liquid monomer containing pure phosphoric acid (250 ppm) hydroquinone (100 ppm) and P-methoxyphenol (1200 ppm). This composition is stable and unchanging we believe for over two years. The container in which Part I is stored requires cleaning and preparation before such stability can be achieved. The liquid monomer of choice for this usage is 2-hexyl cyanoacrylate.

Part II consists of pure powdered gold (5±3 microns), a small amount of prepolymerized polymer of the same cyanoacrylate and ethyl myristate. Any of the large chain fatty acid esters will work to replace ethyl myristate so long as they are liquids.

The pre-polymerized polymers of cyanoacrylate are unstable and change their structures and properties even in the solid state. The change is exponential and therefore the polymer must be used within a limited amount of time before deterioration occurs.

The polymer is prepared by addition of part 1 to a rapidly stirring weak bicarbonate-water solution. The addition must be added drop-wise to avoid unpolymerized masses from forming. The solid polymer is washed thoroughly with pure water to remove any traces of bicarbonate, then washed thoroughly with pure methanol to remove the water. Methanol dries rapidly and when the polymer is further dried at a high reduced pressure for 16–18 hours, it is considered dry. The polymer must be used in the next step within 24 hours to obtain consistent results in the final product. This mixture must be sterilized within 72 hours from the time of preparation.

Part II is sterilized with ethylene oxide gas with the stopper held in an open position. Ethylene oxide is an alkylating agent and after sterilization the prepolymerized polymer is stable. Hence, the stability and sterilization of part 2 are carried out simultaneously. The sterilized samples of Part II are capped in a clean room under sterile handling conditions.

The pre-polymerized polymer can be stabled by treatment with any of the strong alkylating agents, like ethylene oxide, ketene, etc.

This composition of matter has good cohesion as well as adequate adhesion to function well for AVMs and other similar uses within the vascular tree. The cohesion keeps the material together during the time required for it to polymerize. The adhesion makes it stick to the artery walls.

The polymerized device will cause a modest but desirable inflammatory response in the treated tissues.

A Formulation for Arteriovenous Malformations and Tumors

It is desirable to prepare a formulation for the intravascular occlusion of AVMs and Tumors that will have the following properties:

- The product has a very slow rate of biodegradation.
- Both liquid and solid forms should have excellent cohesion.
- The delivered product should have medium adhesion
- The delivered product must be radiopaque.
- The solid polymer should be soft and pliable.
- The delivered product must have a very low or negligible histotoxicity.
- The deposited product must have no long term negative properties such as carcinogenicity, teratogenicity, systemic toxicity or other unpredictable biological and medical effects.
- The products must be sterile.
- The delivered product must have good flow characteristics for selective catheterization.
- The product must be stable on storage for an extended period of time.
- The formulation should be made from pure products and be reproducible for simple manufacturing procedures.

The product formulation is:

Part I (M1)	
2-Hexyl Cyanoacrylate	999,550 ppm
Hydroquinone	100 ppm
p-Methoxyphenol	100 ppm
Pure Phosphoric Acid	250 ppm
Part II (M2)	
Pure Gold	1.0000 g
Pure Ethyl Myristate	0.5000 g
FMS*	0.0200 g

*FMS is a specially prepared polymer of 2-hexyl cyanoacrylate and must be used within 24 hours of preparation or will change and be unusable. Further, it must be sterilized within 72 hours.

Each item of this formulation is critical to the proper performance of the product.

2-Hexyl Cyanoacrylate

This cyanoacrylate homolog was chosen because it biodegrades very slowly in blood or any living tissue. The secondary alcohol will biodegrade several thousand times slower than its primary derivative. This very slow degradation rate also lowers greatly the histotoxicity.

Hydroquinone

When the amount of hydroquinone is reduced by half (50 ppm) the product shows low shelf life stability. Large amounts over 100 ppm do not seem to effect the product stability. This inhibitor lowers the effect of the high energy free radicals that may appear in the cyanoacrylate.

p-Methoxyphenol

The slow polymerization of cyanoacrylates even under refrigeration is caused by low energy free radicals. When 100 ppm of p-methoxyphenol is present this slow polymerization is prevented and long term stability is achieved. Less p-methoxyphenol (50 ppm) will not protect the product.

Sulfur Dioxide

The faintest trace of sulfur dioxide is present in the product. One part per million can be seen and less is present. However, this very faint trace adds to the stability of Neuracryl* ml in the ampule.

Gold

Tantalum, platinum and gold are all radiopaque. Gold was best for us because it could be suspended colloidally in the mixture. One gram of gold is used per device.

Ethyl Myristate

Subbicates, fatty acid esters and other plasticizers, are useful for fastening the polymers of the cyanoacrylates. they also will stabilize the pre-formed polymers of the cyanoacrylates so that they may be used as thickeners. We have chosen ethyl myristate, an esterified, biocompatible fatty acid because of the convenience of purification and analysis and because is works well to give the formulation the desirable properties.

FMS

FMS is the polymer of 2-hexyl cyanoacrylate formed in a weak, aqueous sodium bicarbonate solutions. The polymer differs in structure and size depending on how it is formed. This polymer will remain stable until M2 can be formulated. The polymer must be formed and dried completely before use. The final formulation of M2 must occur within 24 hours because the ethyl myristate stabilized FMS until sterilization can be performed. After sterilization the product is stable for several years.

Neuracryl M

M1 and M2 are mixed immediately before use. The mixture should be used within 4 hours after mixing. If there is a delay, the syringe should be turned over several times a minute to resuspend the gold which will be settled.

What is claimed is:

1. A composition for creating therapeutic vascular occlusions in an animal comprising a mixture of:

(a) Part 1 comprised of 2-hexyl cyanoacrylate, hydroquinone, p-methoxyphenol and phosphoric acid; and

(b) Part 2 comprising gold metal powder, ethyl myristate and a sterilized polymer of 2-hexylcyanoacrylate in weak aqueous bicarbonate solution.

2. The composition of claim 1 wherein Part 1 comprises about 100 PPM hydroquinone, 100 PPM p-methoxyphenol, 250 PPM phosphoric acid and the remainder 2-hexyl cyanoacrylate.

3. The composition of claim 2 wherein Part 2 comprises about 65 percent by weight gold, about 30 percent by weight ethyl myristate and the remainder said sterilized polymer of 2-hexylcyanoacrylate in weak aqueous bicarbonate solution.

4. The composition of claim 1 wherein Part 2 includes sulfur dioxide as a stabilizer.

5. A method for creating therapeutic vascular occlusions in an animal needing therapeutic vascular occlusion comprising the steps of:

(a) Mixing together Part 1 comprised of 2-hexyl cyanoacrylate, hydroquinone, p-methoxyphenol and phosphoric acid with Part 2 comprising gold metal powder, ethyl myristate and a sterilized polymer of 2-hexylcyanoacrylate in weak aqueous bicarbonate solution; and

(b) injecting the mixture into a vascular site needing occlusion with the gold metal powder suspended in the mixture.

* * * * *